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Extracorporeal Shockwave Therapy in Osteonecrosis of the Femoral Head: Where Do We Stand?

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Abstract

Osteonecrosis of the femoral head (ONFH) is a progressive disease characterized by ischemic lesions and structural damage in the head of the femur caused by insufficient blood supply due to multiple etiologies. As a safe, effective, non-invasive, and low-cost treatment strategy, Extracorporeal Shockwave Treatment (ESWT) is now widely applied in musculoskeletal disorders such as delayed bone healing, bone marrow edema (BME), knee osteoarthritis, and certain types of avascular bone necrosis. ESWT may promote vascularization and osteogenesis through a cascade reaction stimulated by the transformation of physical energy, promoting tissue regeneration, and repair. ESWT is recommended in treating early-stage ONFH.

Keywords: Shock waves; ESWT, Femoral head osteonecrosis

Introduction

Osteonecrosis of the femoral head (ONFH) is a progressive disease characterized by ischemic lesions and structural damage in the head of the femur caused by insufficient blood supply due to multiple etiologies. Without proper intervention, ONFH may cause arthralgia, activity limitation, and arthritis, eventually leading to disability [1]. Given its relatively high incidence rate among young- and middle-aged adults, this may impose a significant economic burden on both patients and society. Therefore, non-invasive treatment in the early stages of the disorder is considerably important when it comes to minimizing the suffering and burden of the patient.

Extracorporeal shockwave therapy (ESWT) has gained much attention in the past decade due to its promising clinical performance and increasing research evidence [2]. Extracorporeal shockwave (ESW) is a type of discontinuous mechanical wave with low frequency, short period, and high-energy density. This acoustic wave is then transformed into mechanical pressure, which acts on cells and tissues, producing biological changes. As a safe, effective, non-invasive, and low-cost treatment strategy, ESWT is now widely applied in musculoskeletal disorders such as delayed bone healing, bone marrow edema (BME), knee osteoarthritis, and certain types of avascular bone necrosis. However, the mechanism behind ESWT remains vague; some of the latest clinical research and misunderstandings still need to be discussed and clarified.

Mechanism of ESWT in Treating ONFH

While numerous studies have delved into unraveling the mechanism of ESWT, much of the truth remains veiled. Haupt's traditional theory categorizes the therapeutic process into four distinct phases: the physical phase, subsequent physical-chemical phase, chemical phase, and biological phase [3]. In the physical phase, ESW is generated and passes through various layers of body tissues, inducing molecule ionizations and augmenting the permeability of cell membranes. This sets the stage for the subsequent physical–chemical phase, where diffusible radicals and biomolecule interactions unfold, giving rise to intracellular reactions and molecular changes. The ensuing chemical phase witnesses an escalation in the production of various cytokines and growth factors. Finally, the biological phase unfolds, eliciting a spectrum of biological effects, including chondroprotection, neovascularization, anti-inflammation, anti-apoptosis, and tissue regeneration.

Throughout this process, ESW is generated and traverses diverse layers of body tissues, inducing molecule ionizations and enhancing cell membrane permeability by transferring energy through extracellular cavitations, pressure gradients, and temperature changes [4]. Subsequently, diffusible radicals and biomolecule interactions come into play, instigating

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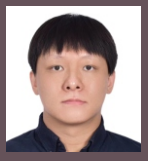
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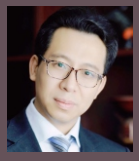
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intracellular reactions and molecular alterations that manifest in diverse biological effects. Early studies pointed to chondroprotection, neovascularization, anti-inflammation, anti-apoptosis, and tissue regeneration as some of these effects [5]. Recent investigation have further substantiated these findings, providing new evidence that supports hypotheses regarding the transformation from physical energy to biological responses.

Previous studies elucidated that ESWT may promote neovascularization and bone regeneration by increasing the level of certain factors such as vessel endothelial growth factor (VEGF), proliferating cell nuclear antigen (PCNA), and bone morphogenic protein-2 (BMP-2) while downregulating certain anti-inflammatory factors [6, 7]. Yet, the latest studies have given us insights into other possible answers. Wu et al. [8] conducted both in vivo and in vitro studies examining the therapeutic effect of ESWT on endothelial cells with steroid-induced ONFH. The outcome demonstrated that ESWT promotes proliferation, migration, and angiogenesis while attenuating apoptosis both in vivo and in vitro. The in vitro experiment also indicated that miR-135b downregulation and the over-expression of its potential target gene FOXO1 were observed to weaken the positive effect of ESWT. Another study conducted by Li et al. [9] focusing on osteoporosis suggested that ESWT stimulated the differentiation of osteoblasts in vitro while increasing bone formation in rabbit models through the TGF-β/SMAD2 pathway. Hsu et al. [10] examined the level of pro-inflammatory cytokines in ONFH rats with or without ESWT. Results showed that ESWT is proven to improve articular cartilage and subchondral bone by upregulating IL33 and its receptor ST2 meanwhile downregulating certain pro-inflammatory cytokines such as IL5, IL6, and IL17A. Concurrently, the study indicated that the decrease of hypertrophic chondrocytes and increase of structural integrity also contribute to the protection of articular cartilage and subchondral bone.

The potential mechanism underlying ESWT can be succinctly summarized: ESW traverses layers of tissue, generating substantial velocity and pressure within the femoral head, leading to mechanical damage and subsequent tissue restoration. This dynamic process predominantly occurs at sites characterized by rapid impedance changes, such as the interface between bone and soft tissue or the sclerotic rim of ONFH. Following these alterations, ESW undergoes energy deposition at diverse interfaces between normal and necrotic tissues, inducing a cascade of biochemical and molecular responses in the femoral head. This cascade effect may lead to vascularization and osteogenesis, fostering tissue regeneration and repair. Furthermore, ESW possesses the capacity to recruit stem cells and prompt cell differentiation, potentially contributing to osteogenesis and angiogenesis [11].

In Addition, ESWT Exhibits the Following Effects

Neovascularization and bone regeneration

ESWT enhances these processes by modulating the levels of specific factors such as VEGF, PCNA, and BMP-2, while concurrently suppressing anti-inflammatory factors.

Endothelial cell proliferation and migration

ESWT promotes these processes, particularly in cases of steroid-induced ONFH.

Osteoblast differentiation

In vitro studies reveal that ESWT stimulates this process and augments bone formation in rabbit models, achieved through the TGF-B/SMAD2 pathway.

Protection of articular cartilage and subchondral bone

ESWT demonstrates efficacy in improving these areas by modulating specific pro-inflammatory cytokines such as IL33 and its receptor ST2, while concurrently downregulating others such as IL5, IL6, and IL17A.

These multifaceted effects underscore the potential of ESWT as a comprehensive therapeutic intervention for ONFH, impacting various facets of tissue repair, regeneration, and inflammation modulation.

Clinical Performance of ESWT in Treating ONFH

ESW was initially introduced to treat renal calculus in 1980. Twenty-one years later, Ludwig et al[12]. proposed the possibility of applying ESW as a non-invasive therapeutic strategy for ONFH. After decades of research and clinical application, the 2021 Consensus statement on ESWT indications and contraindications by the International Society for Medical Shockwave Treatment has approved avascular bone necrosis without articular derangement as a standard indication [12].

New evidence has emerged over the years to support the clinical application of ESWT in treating ONFH. Our shockwave medicine center at China–Japan Friendship Hospital (CJFH) has also accumulated significant experience and cases. Gao et al. [13] retrospectively examined the treatment outcomes of 335 ONFH patients involving 528 hips. All patients underwent two sessions of focused ESWT, resulting in a significant improvement in pain score and Harris hip score after treatment. Most patients described a substantial improvement in daily life function, mainly attributable to pain reduction. A decreasing trend was observed in lesion size, and the reduction of BME was considered significant. No systematic or neurovascular complications were observed, except for mild local swelling and erythema resolving within days. This study suggests that ESWT is effective for early-stage ONFH in the short term with minimal complications, consistent with findings in leukemia patients. Sun et al. [14] recruited 43 patients (86 hips) with early-stage ONFH in adult survivors with leukemia who received allogeneic hematopoietic stem cell transplantation. All participants received two sessions of ESWT, with 89.5% of hips showing pain reduction and an increase in mean HHS score. Only 2 hips required total hip arthroplasty at the 12-month follow-up. A significant reduction in BME and a trend of lesion size decrease were observed. Early prevention of glucocorticoid-induced ONFH is also crucial. In Yang et al.'s study [15], 153 patients who had received high-dose glucocorticoid treatment were randomly allocated into two groups. One group received a single session of high-energy focused ESWT (HF-ESWT), while the other received none. Both groups were administered alendronate sodium tablets and Fufang Xian Ling GU Bao. Significant differences were found in bilateral hip function at 6-month and 12-month follow-

ups. Eleven patients were diagnosed with ONFH during follow-up, and a significant difference was observed, with only 2 of the ONFH patients treated with HF-ESWT. The rest were not. The results reveal the notable potential of ESWT in preventing glucocorticoid-induced ONFH.

Our focus on this issue is not unique. Xie et al. [16] revised 39 consecutive patients (53 hips) with nontraumatic, ARCO stage I to III ONFH treated with a single session of ESWT. The outcomes showed a significant improvement in Harris hip Score and VAS score, with clinical success rates of 87.5%, 71.4%, and 75.0% in ARCO stage I, II, and III patients. The results suggest that ESWT is effective in treating nontraumatic ONFH, especially for patients in the early stages of the disorder. BME is commonly seen in ONFH patients. In Zhao et al.'s study [17], 67 patients with BME caused by ONFH were presented with personalized ESWT during rehabilitation. MRI shows a decrease in BME sizes in 98.5% of all cases, along with improvements in Harris hip score and Charnley score. In another study conducted by Alkhawashki et al. [18], 24 patients received two sessions of ESWT for ONFH, showing improvement in both joint function and pain. The results favor the application of ESWT in ONFH treatment.

Misapprehensions and Challenges

Despite the rapid development of ESWT in recent years, some misapprehensions still require clarification. ESWT can be characterized as focused and radial due to different types of generating devices. Multiple pieces of evidence favor the application of focused shockwave in the treatment of ONFH [19]. Although radial pressure wave (RPW) is also capable of generating extracellular cavitations, its intensity decreases by more than 50% for every centimeter of tissue penetration [20]. Therefore, it is difficult for RPW to achieve therapeutic effects on deep tissues such as the femoral head. Even so, there is still evidence showing that RPW may help to reduce pain and improve hip function. We believe this is because of its effect on surrounding soft tissues such as the joint capsule rather than acting on the bone itself.

Recent studies suggest that ESWT may be dosage dependent. A systematic review conducted by Abbas et al. analyzed the dose-dependent effects of ESWT on pain and function in ONFH. The review included 13 articles, of which 8 articles were cohort studies, 4 were RCT, and 1 was a case–control study. The author elucidated that whereas ESWT of all energy levels is effective in managing pain and function while delaying further progression of the disease, medium- and low-energy densities were less prevailing [19]. This finding is consistent with our experience in the center. It is essential to apply high-energy densities during treatment to promote tissue restoration, namely flux density of >0.3 mJ/mm2 with more than 8000–10,000 shocks per session.

Despite its efficacy in treating early-stage ONFH, ESWT still lacks the capability of curing ONFH of all types and etiology. Different studies have demonstrated the application and outcome of ESWT depend on disease stages. Surgical intervention is often required for patients in the peri-collapse period, especially those who are classified as type L3 by the CJFH classification and ARCO stage III or above. The application of ESW can be taken as part of the cocktail therapy to relieve pain and promote tissue repair. We should notice that although previous studies and our experience in the center suggest that ESWT is a safe therapeutic intervention with little complications, there is still evidence showing that potential risks and contradictions still exist [12]. Practitioners should be familiar with hip joint anatomy to avoid secondary injuries.

As an ancient Chinese proverb goes, "Time passes quickly like a white pony's shadow across a crevice." It has been more than two decades since the first report of ESWT. Although a great number of research studies have come out during the years, the mechanism of ESWT in ONFH treatment still lacks consensus. Most studies on clinical performance are single-centered, retrospective studies. These are the real challenges we are facing at the moment. Institutions and companies have begun to question the scientific evidence behind shock waves [21,22]. Continuous and systematic research is needed, including in vitro and in vivo experiments, studies with animal models, and cellular molecular experiments. Multicenter, double-blind designed research with a large sample size and long-term follow-up is also in demand to provide sufficient evidence for ESWT.

Conclusion

ESWT is a safe, effective, non-invasive therapeutic strategy for ONFH treatment. ESWT may promote vascularization and osteogenesis through a cascade reaction stimulated by the transformation of physical energy, promoting tissue regeneration, and repair. HF-ESWT is recommended in treating early-stage ONFH. Recent studies have proved the efficacy of ESWT in treating early-stage ONFH. However, studies of high quality are still needed to clarify the mechanisms and clinical principles. Future research on clinical performances should focus on multicenter, double-blind design with a large sample size and long-term follow-up is to provide high-quality evidence for ESWT.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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References

1. Mont MA, Salem HS, Piuzzi NS, Goodman SB, Jones LC. Nontraumatic osteonecrosis of the femoral head: Where do we stand today? A 5-year update. J Bone Joint Surg Am 2020;102:1084-99.

2. Zhang Q, Liu L, Sun W, Gao F, Cheng L, Li Z. Extracorporeal shockwave therapy in osteonecrosis of femoral head: A

systematic review of now available clinical evidences. Medicine (Baltimore) 2017;96:e5897.

3. Haupt G. Use of extracorporeal shock waves in the treatment of pseudarthrosis, tendinopathy and other orthopedic diseases. J Urol 1997;158:4-11.

4. Auersperg V, Trieb K. Extracorporeal shock wave therapy: An update. EFORT Open Rev 2020;5:584-92.

5. Moya D, Ramón S, Schaden W, Wang CJ, Guiloff L, Cheng JH. The role of extracorporeal shockwave treatment in musculoskeletal disorders. J Bone Joint Surg Am 2018;100:251-63.

6. Wang QW, Zhang QY, Gao FQ, Sun W. Focused extracorporeal shockwave treatment during early stage of osteonecrosis of femoral head. Chin Med J (Engl) 2019;132:1867-9.

7. Cheng JH, Wang CJ. Biological mechanism of shockwave in bone. Int J Surg 2015;24:143-6.

8. Wu X, Wang Y, Fan X, Xu X, Sun W. Extracorporeal shockwave relieves endothelial injury and dysfunction in steroid-induced osteonecrosis of the femoral head via miR-135b targeting FOXO1: In vitro and in vivo studies. Aging (Albany NY) 2022;14:410-29.

9. Li B, Wang R, Huang X, Ou Y, Jia Z, Lin S, et al. Extracorporeal shock wave therapy promotes osteogenic differentiation in a rabbit osteoporosis model. Front Endocrinol (Lausanne) 2021;12:627718.

10. Hsu SL, Jhan SW, Hsu CC, Wu YN, Wu KL, Kuo CA, et al. Effect of three clinical therapies on cytokines modulation in the hip articular cartilage and bone improvement in rat early osteonecrosis of the femoral head. Biomed J 2022;46:100571.

11. Sun W, Li Z. Extracorporeal shockwave therapy for osteonecrosis of femoral head: Traps and challenges. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2019;33:659-61.

12. Ludwig J, Lauber S, Lauber HJ, Dreisilker U, Raedel R, Hotzinger H. High-energy shock wave treatment of femoral head necrosis in adults. Clin Orthop Relat Res 2001:119-26.

13. Qu RD, Sun W. Interpretation of international society for medical shockwave treatment consensus-2021 in diagnosis and treatment of musculoskeletal diseases. Chin J Gen Pract 2022;21:826-30.

14. Gao F, Sun W, Li Z, Guo W, Wang W, Cheng L, et al. High-energy extracorporeal shock wave for early stage osteonecrosis of the femoral head: A single-center case series. Evid Based Complement Alternat Med 2015;2015:468090.

15. Sun W, Gao F, Guo W, Wang B, Li Z, Cheng L, et al. Focused extracorporeal shock wave for osteonecrosis of the femoral head with leukemia after allo-HSCT: A case series. Bone Marrow Transplant 2016;51:1507-9.

16. Yang X, Shi L, Zhang T, Gao F, Sun W, Wang P, et al. High-energy focused extracorporeal shock wave prevents the occurrence of glucocorticoid-induced osteonecrosis of the femoral head: A prospective randomized controlled trial. J Orthop Translat 2022;36:145-51.

17. Xie K, Mao Y, Qu X, Dai K, Jia Q, Zhu Z, et al. High-energy extracorporeal shock wave therapy for nontraumatic osteonecrosis of the femoral head. J Orthop Surg Res 2018;13:25.

18. Zhao W, Gao Y, Zhang S, Liu Z, He L, Zhang D, et al. Extracorporeal shock wave therapy for bone marrow edema syndrome in patients with osteonecrosis of the femoral head: A retrospective cohort study. J Orthop Surg Res 2021;16:21.

19. Alkhawashki HM, Al-Boukai AA, Al-Harbi MS, Al-Rumaih MH, Al-Khawashki MH. The use of extracorporeal shock wave therapy (ESWT) in treating osteonecrosis of the femoral head (AVNFH): A retrospective study. Int Orthop 2023;47:2953-60.

20. Abbas A, Khan Z, Veqar Z. Dose dependent effects of extracorporeal shockwave therapy on pain and function in osteonecrosis of femoral head: A systematic review. J Clin Orthop Trauma 2023;45:102275.

21. Császár NB, Angstman NB, Milz S, Sprecher CM, Kobel P, Farhat M, et al. Radial shock wave devices generate cavitation. PLoS One 2015;10:e0140541.

22. Moya D, Sun W, Simplicio C, Guiloff L, Kwangsun P, Giorno A, et al. Scientific evidence of shock waves in orthopedics and traumatology: It is time to set the record straight. J Regen Sci 2023;3:1-6.

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